

Claims

1. A contrast agent for diagnostic imaging in the form of an aqueous suspension of microvesicles of a gas stabilized by a layer of film-forming surfactant, said suspension being obtainable by reconstitution in a physiologically acceptable aqueous carrier of a dried material comprising at least one film-forming surfactant and being exposed to a gas, wherein, prior to said reconstitution, said material is exposed to an atmosphere of said gas having a pressure lower than atmospheric pressure.
2. A contrast agent according to claim 1 wherein the pressure of said gas is from about 100 to about 900 mbar.
3. A contrast agent according to claim 1 wherein the pressure of said gas is from about 300 to 700 mbar.
4. A contrast agent according to claim 1 wherein the pressure of said gas is from about 400 to 600 mbar.
5. A contrast agent according to claim 1 wherein the dried material is a lyophilized material.
6. A contrast agent according to claim 1 wherein said dried material is contained in a container which undergoes to vacuum before the gas is contacted with said material.
7. A contrast agent according to claim 1 wherein the gas is selected from the group consisting of halogenated gases, air, nitrogen, carbon dioxide, helium, krypton, xenon, argon, methane, hyperpolarized gases, hyperpolarized noble gases, radioactive gases and mixtures thereof.
8. A contrast agent according to claim 7 wherein the halogenated gas is a perfluorinated gas.
9. A contrast agent according to claim 8 wherein the perfluorinated gas is selected from the group consisting of perfluoromethane, perfluoroethane, perfluoropropane, perfluorobutanes, perfluoropentanes, perfluorohexanes, perfluoroheptanes, perfluoropropene, perfluorobutenes, perfluorobutadiene, perfluorobut-2-yne, perfluorocyclobutane, perfluoromethylcyclobutane, perfluorodimethylcyclobutanes, perfluorotrimethylcyclobutanes, perfluorocyclopentane, perfluoromethylcyclopentane,

perfluorodimethylcyclopentanes, perfluorocyclohexane,
perfluoromethylcyclohexane, perfluorocycloheptane, sulfur hexafluoride and
mixtures thereof.

10. A contrast agent according to claim 7 wherein hyperpolarized gas is selected
5 from the group consisting of hyperpolarized helium, hyperpolarized xenon,
hyperpolarized neon and mixtures thereof.

11. A contrast agent according to claim 1 wherein said film-forming surfactant
comprises a phospholipid.

12. A contrast agent according to claim 11 wherein said phospholipid is
10 selected from the group consisting of a saturated phospholipid, a synthetic non-
saturated phospholipid and mixtures thereof.

13. A contrast agent according to claim 12, wherein the saturated phospholipid
is selected from the group consisting of dilauryloyl-phosphatidylcholine (DLPC),
dimyristoylphosphatidylcholine (DMPC), dipalmitoyl-phosphatidylcholine (DPPC),
15 diarachidoylphosphatidylcholine (DAPC), distearoyl-phosphatidylcholine (DSPC),
dioleoylphosphatidylcholine (DOPC), 1,2 Distearoyl-sn-glycero-3-
Ethylphosphocholine (Ethyl-DSPC), dipentadecanoylphosphatidylcholine
(DPDPC), 1-myristoyl-2-palmitoylphosphatidylcholine (MPPC), 1-palmitoyl-2-
myristoylphosphatidylcholine (PMPC), 1-palmitoyl-2-stearoylphosphatid-
ylcholine (PSPC), 1-stearoyl-2-palmitoyl-phosphatidylcholine (SPPC),), 1-
20 palmitoyl-2-oleylphosphatidylcholine (POPC), 1-oleyl-2-palmitoyl-
phosphatidylcholine (OPPC), dilauryloyl-phosphatidylglycerol (DLPG) and its
alkali metal salts, diarachidoylphosphatidylglycerol (DAPG) and its alkali metal
salts, dimyristoylphosphatidylglycerol (DMPG) and its alkali metal salts,
25 dipalmitoyl-phosphatidylglycerol ("DPPG") and its alkali metal salts,
distearoylphosphatidylglycerol (DSPG) and its alkali metal salts,
dioleoylphosphatidylglycerol (DOPG) and its alkali metal salts, dimyristoyl
phosphatidic acid (DMPA) and its alkali metal salts, dipalmitoyl phosphatidic
acid "DPPA) and its alkali metal salts, distearoyl phosphatidic acid (DSPA),
30 diarachidoyl phosphatidic acid (DAPA) and its alkali metal salts, dimyristoyl
phosphatidyl-ethanolamine (DMPE), dipalmitoyl phosphatidylethanolamine
(DPPE), DPPE-PEG, distearoyl phosphatidyl-ethanolamine (DSPE), DSPE-PEG,
dioleoylphosphatidylethanolamine (DOPE), diarachidoylphosphatidylethanolamine
(DAPE), dilinoleylphosphatidylethanolamine (DLPE), dimyristoyl
35 phosphatidylserine (DMPS), diarachidoyl phosphatidylserine (DAPS),

dipalmitoyl phosphatidylserine (DPPS), distearoylphosphatidylserine (DSPS), dioleoylphosphatidylserine (DOPS), dipalmitoyl sphingomyelin (DPSP), distearoyl sphingomyelin (DSSP) and mixtures thereof.

14. A contrast agent according to claim 11, wherein said dried material further
5 comprises viscosity enhancers or stabilizers selected from linear and cross-linked poly- and oligo-saccharides, sugars, hydrophilic polymers like polyoxypropylene glycol and polyoxyethylene glycol.

15. The contrast agent of claim 11, wherein said dried material further
10 comprises up to 50% by weight of a surfactants selected from fatty acids, esters and ethers of fatty acids and alcohols with polyols.

16. A composition for preparing a contrast agent in the form of an aqueous suspension containing gas-filled microvesicles useful in diagnostic imaging, said composition comprising: a) a dried material comprising at least one film-forming surfactant and b) a gas in contact with said dried material, said composition being
15 reconstitutable upon contact with a physiologically acceptable aqueous carrier to form said gas-filled microvesicles suspension, wherein said gas has a pressure lower than atmospheric pressure.

17. A composition according to claim 16 wherein the dried material is a lyophilized material.

20 18. A composition according to claim 16 wherein the reduced pressure of said gas introduced into said container comprises between about 100 and about 900 mbar.

19. A composition according to claim 16 wherein the reduced pressure of said gas introduced into said container comprises between about 300 and about 700
25 mbar.

20. A composition according to claim 16 wherein the reduced pressure of said gas introduced into said container comprises between about 400 and about 600 mbar.

21. A composition according to claim 16, wherein the gas is selected from the
30 group consisting of halogenated hydrocarbon gases, air, nitrogen, carbon dioxide, helium, krypton, xenon, argon, methane, radioactive gases, hyperpolarized gases and mixtures thereof.

22. A composition according to claim 21, wherein said film-forming surfactant comprises a saturated phospholipid or a synthetic non-saturated phospholipid or mixtures thereof.

23. A composition according to claim 22, wherein the saturated phospholipid is
5 selected from the group consisting of dilauryloyl-phosphatidylcholine (DLPC), dimyristoylphosphatidylcholine (DMPC), dipalmitoyl-phosphatidylcholine (DPPC), diarachidoylphosphatidylcholine (DAPC), distearoyl-phosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), 1,2 Distearoyl-sn-glycero-3-Ethylphosphocholine (Ethyl-DSPC), dipentadecanoylphosphatidylcholine
10 (DPDPC), 1-myristoyl-2-palmitoylphosphatidylcholine (MPPC), 1-palmitoyl-2-myristoylphosphatidylcholine (PMPC), 1-palmitoyl-2-stearoylphosphatidylcholine (PSPC), 1-stearoyl-2-palmitoyl-phosphatidylcholine (SPPC), 1-palmitoyl-2-oleylphosphatidylcholine (POPC), 1-oleyl-2-palmitoyl-phosphatidylcholine (OPPC), dilauryloyl-phosphatidylglycerol (DLPG) and its
15 alkali metal salts, diarachidoylphosphatidylglycerol (DAPG) and its alkali metal salts, dimyristoylphosphatidylglycerol (DMPG) and its alkali metal salts, dipalmitoyl-phosphatidylglycerol ("DPPG") and its alkali metal salts, distearoylphosphatidylglycerol (DSPG) and its alkali metal salts, dioleoylphosphatidylglycerol (DOPG) and its alkali metal salts, dimyristoyl
20 phosphatidic acid (DMPA) and its alkali metal salts, dipalmitoyl phosphatidic acid "DPPA) and its alkali metal salts, distearoyl phosphatidic acid (DSPA), diarachidoyl phosphatidic acid (DAPA) and its alkali metal salts, dimyristoyl phosphatidyl-ethanolamine (DMPE), dipalmitoyl phosphatidylethanolamine (DPPE), DPPE-PEG, distearoyl phosphatidyl-ethanolamine (DSPE), DSPE-PEG,
25 dioleoylphosphatidylethanolamine (DOPE), diarachidoylphosphatidylethanolamine (DAPE), dilinoleylphosphatidylethanolamine (DLPE), dimyristoyl phosphatidylserine (DMPS), diarachidoyl phosphatidylserine (DAPS), dipalmitoyl phosphatidylserine (DPPS), distearoylphosphatidylserine (DSPS), dioleoylphosphatidylserine (DOPS), dipalmitoyl sphingomyelin (DPSP), distearoyl
30 sphingomyelin (DSSP) and mixtures thereof.

24. A container for use in preparing a gas containing contrast agent for diagnostic imaging, said container comprising

a dried material comprising at least one film forming surfactant; and
a gas;

35 wherein said gas is present at a pressure lower than atmospheric pressure.

25. A container according to claim 24, wherein the gas is present at a pressure of from about 100 to about 900 mbar.

26. A container according to claim 24, wherein the gas or gas mixture is present at a pressure of from about 300 to about 700 mbar.

5 27. A container according to claim 24, wherein the gas or gas mixture is present at a pressure of from about 400 to about 600 mbar.

28. A container according to claim 24 wherein the dried material is a lyophilized material.

29. A container according to claim 24, wherein the gas is selected from the group consisting of halogenated hydrocarbon gases, air, nitrogen, carbon dioxide, helium, krypton, xenon, argon, methane, radioactive gases, hyperpolarized gases and mixtures thereof.

30. A container according to claim 24, wherein said film-forming surfactant comprises a saturated phospholipid or a synthetic non-saturated phospholipid or mixtures thereof.

31. A container according to claim 24, wherein the saturated phospholipid is selected from is selected from the group consisting of dilauryloyl-phosphatidylcholine (DLPC), dimyristoylphosphatidylcholine (DMPC), dipalmitoyl-phosphatidylcholine (DPPC), diarachidoylphosphatidylcholine (DAPC), distearoyl-phosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), 1,2 Distearoyl-sn-glycero-3-Ethylphosphocholine (Ethyl-DSPC), dipentadecanoylphosphatidylcholine (DPDPC), 1-myristoyl-2-palmitoylphosphatidylcholine (MPPC), 1-palmitoyl-2-myristoylphosphatidylcholine (PMPC), 1-palmitoyl-2-stearoylphosphatidylcholine (PSPC), 1-stearoyl-2-palmitoyl-phosphatidylcholine (SPPC),), 1-palmitoyl-2-oleylphosphatidylcholine (POPC), 1-oleyl-2-palmitoyl-phosphatidylcholine (OPPC), dilauryloyl-phosphatidylglycerol (DLPG) and its alkali metal salts, diarachidoylphosphatidylglycerol (DAPG) and its alkali metal salts, dimyristoylphosphatidylglycerol (DMPG) and its alkali metal salts, dipalmitoyl-phosphatidylglycerol ("DPPG") and its alkali metal salts, distearoylphosphatidylglycerol (DSPG) and its alkali metal salts, dioleoylphosphatidylglycerol (DOPG) and its alkali metal salts, dimyristoyl phosphatidic acid (DMPA) and its alkali metal salts, dipalmitoyl phosphatidic acid "DPPA) and its alkali metal salts, distearoyl phosphatidic acid (DSPA), diarachidoyl phosphatidic acid (DAPA) and its alkali metal salts, dimyristoyl phosphatidyl-ethanolamine (DMPE), dipalmitoyl phosphatidylethanolamine

(DPPE), DPPE-PEG, distearoyl phosphatidyl-ethanolamine (DSPE), DSPE-PEG, dioleoylphosphatidylethanolamine (DOPE), diarachidoylphosphatidylethanolamine (DAPE), dilinoleoylphosphatidylethanolamine (DLPE), dimyristoyl phosphatidylserine (DMPS), diarachidoyl phosphatidylserine (DAPS),
 5 dipalmitoyl phosphatidylserine (DPPS), distearoylphosphatidylserine (DSPS), dioleoylphosphatidylserine (DOPS), dipalmitoyl sphingomyelin (DPSP), distearoyl sphingomyelin (DSSP) and mixtures thereof.

32. A two component kit comprising, as the first component, a composition as claimed in any of the claims from 16 to 22 and, as the second component a
 10 physiologically acceptable carrier liquid which, when admixed with the first component, provides an injectable ultrasound or magnetic resonance contrast agent.

33. A process for the manufacture of a composition as claimed in any of the claims from 16 to 22 to claim 16 which comprises the steps of:

- a) preparing a dried material comprising at least one film-forming surfactant
 15 into a container;
- b) applying a vacuum to said container;
- c) introducing a gas into said container, up to a pressure which is lower than atmospheric pressure;
- d) effecting a sealing closure of said container, thus obtaining the dried material
 20 in contact with an atmosphere of said gas having a pressure lower than atmospheric pressure.

34. The process of claim 33 wherein the gas is introduced into said container up to a pressure of from about 100 to 900 mbar.

35. The process of claim 33 wherein the gas is introduced into said container up
 25 to a pressure of from about 300 to 700 mbar.

36. The process of claim 33 wherein the gas is introduced into said container up to a pressure of from about 400 to 600 mbar.

37. The process according to claim 33 wherein the gas is selected from the group consisting of halogenated hydrocarbon gases, air, nitrogen, carbon dioxide,
 30 helium, krypton, xenon, argon, methane, radioactive gases, hyperpolarized gases and mixtures thereof.

38. The process according to claim 33 wherein said film-forming surfactant comprises a saturated phospholipid or a synthetic non-saturated phospholipid or mixtures thereof.

5 39. The process of claim 28, wherein the saturated phospholipid is selected from phosphatidic acid, phosphatidylcholine, phosphatidyl-ethanolamine, phosphatidyl-serine, phosphatidylglycerol, phosphatidyl-inositol, cardiolipin, sphingomyelin and mixtures thereof.

40. The process of claim 23, wherein said lyophilised material further comprises viscosity enhancers or stabilizers selected from linear and cross-linked
10 poly- and oligo-saccharides, sugars, hydrophilic polymers like polyoxypropylene glycol and polyoxyethylene glycol.

41. The process of claim 38, wherein said lyophilised material further comprises up to 50% by weight of a surfactant selected from fatty acids, esters and ethers of fatty acids and alcohols with polyols.

15 42. A method of diagnostic imaging which comprises administering to a subject a contrast-enhancing amount of a contrast agent according to claims 1 to 15 and imaging at least a part of said subject.

43. A method according to claim 42 wherein an ultrasound image of said subject is generated.

20 44. A method according to claim 42 wherein a MR image of said subject is generated.

45 A method according to claim 42 wherein a scintigraphic image of said subject is generated.

25 46 The method according to claims 42 to 45 wherein said subject is a vertebrate and said contrast agent is introduced into the vasculature or into a body cavity of said vertebrate.

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